Adjuvant Chemotherapy for Non-small Cell Lung Cancer

Practice Patterns and Outcomes in the General Population of Ontario, Canada

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Background: Adjuvant chemotherapy (ACT) is known to improve survival in patients with early-stage non-small cell lung cancer. Herein, we describe chemotherapy regimens used, dose modifications, survival, and treatment-related toxicity in the general population.

Methods: All cases of non-small cell lung cancer diagnosed in Ontario in the period 2004–2006 who underwent surgical resection ($n = 3354$) were identified using the Ontario Cancer Registry in this population-based retrospective cohort study. We linked electronic records of treatment to the registry to identify all cases treated with ACT ($n = 1032$) and describe drugs, regimens, and dosages delivered. As a proxy measure of ACT-related toxicity, we evaluated deaths and hospitalizations within 16 weeks of starting ACT. Factors associated with dose modification were evaluated by logistic regression. The Cox proportional hazards model was used to describe associations between patient-, disease-, and treatment-related factors and survival.

Results: ACT regimens were identified for 584 of 1032 ACT cases. Almost all cases included cisplatin- or carboplatin-based regimens (478/584, 82%, and 99/584, 17%, respectively). The most common regimen was a vinroelbine/cisplatin doublet (412/584, 71%); 64% of these cases had a dose reduction or omission. Dose modification was not associated with inferior survival on multivariate analysis. Twelve percent of all ACT cases were admitted to hospital within 16 weeks of starting ACT, and there was a 1.6% death rate potentially attributable to ACT. Survival of all ACT cases was comparable with outcomes reported in clinical trials.

Conclusions: ACT regimens used, toxicity, and survival outcomes in the general population are comparable with those reported in clinical trials. Dose modifications used in clinical practice are not associated with inferior survival.

Key Words: Lung cancer, Chemotherapy, Outcomes research, Practice patterns, Comparative effectiveness.

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In 2004, several large randomized controlled trials (RCTs) reported that adjuvant chemotherapy (ACT) improved survival substantially for patients with resected non-small cell lung cancer (NSCLC) compared with observation alone.[1] Since then, adjuvant cisplatin-based chemotherapy has become a standard for eligible patients who undergo resection of NSCLC. Recently, we reported the uptake of ACT for NSCLC in a population-based study in Ontario, Canada.[2] ACT was widely adopted from 2004 onward and was not associated with any increase in hospitalization rates. Moreover, survival at the population level improved after 2004 consistent with the results of clinical trials.

Within the relevant RCTs, there was significant variability in drugs used, dosages, and schedules. Based on the landmark JBR.10 and Adjuvant Navelbine International Trialists Association (ANITA) trials,[3,4] together with results of meta-analyses,[5,6] a vinorelbine-cisplatin doublet has been established as a standard regimen for use in the adjuvant setting for NSCLC. However, the dosing schedules used in both JBR.10 and ANITA were associated with substantial hematological toxicity and poor compliance.[7] Although recent work has demonstrated improved outcomes with the uptake of ACT in the general population,[2] important questions remain regarding regimens used, toxicity, and timing of adjuvant therapy in the "real world." The objectives of the

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current report are to (1) describe chemotherapy drugs/regimens used and treatment-related toxicity in the general population, and (2) explore factors associated with dose modification and its impact on outcome. To address these objectives, we report in detail the use of ACT among all patients who underwent surgical resection of NSCLC in Ontario from 2004 to 2006.

METHODS

Study Design and Population

This report represents a substudy of a larger population-based, retrospective cohort study that compared the management and outcome of early-stage NSCLC in the Canadian province of Ontario before and after 2004.[2] Ontario has a population of approximately 11.4 million people and a single-payer universal health insurance program. The primary study population included all incident cases of NSCLC diagnosed in Ontario from 2001 to 2006 who underwent surgical resection within 24 weeks of diagnosis. Cases treated with preoperative radiotherapy (RT) and/or neoadjuvant chemotherapy (both defined as treatment given between dates of diagnosis and surgery) were excluded. Detailed methods and primary results have been reported previously.[2] In an effort to describe administration of ACT in the contemporary era, this report includes all cases diagnosed during the period 2004–2006 (n = 3354); unless otherwise specified, all results pertain to cases diagnosed within this time period.

Data Sources

The Ontario Cancer Registry (OCR) is a passive, population-based cancer registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer diagnosed in the province of Ontario.[1,8,9] The OCR provided the following information: International Classification of Disease (ICD), version 9 code; the ICD for Oncology histology code; age, sex, place of residence; and date of death. Complete information about vital status was available up to October 2008. The OCR does not compile information about extent of disease or treatment. Indicators of the socioeconomic status of the community in which patients resided at time of diagnosis were linked to the OCR as described previously.[10] Quintiles (Q) of the median household income were based on the household income distribution for the full province of Ontario. Q1 represents the communities where the poorest 20% of the Ontario population resided.

A variety of electronic administrative health databases were linked to the OCR. Records of hospitalization from the Canadian Institute for Health Information provided information about surgical interventions and hospital care. Hospital participation in collection of separation records is known to be consistent and complete throughout Ontario.[11] Physicians in Ontario submit billing codes for chemotherapy to the Ontario Health Insurance Plan (OHIP) for remuneration. Physician billing codes for chemotherapy from the OHIP database were linked to the study database allowing us to identify which patients received chemotherapy (but not the drug/regimen name) and the date of treatment for all patients in the province. The clinical databases of Ontario's eight comprehensive Regional Cancer Centers (RCCs) and Princess Margaret Hospital (PMH) provided detailed records of chemotherapy (including drug and dose) and RT delivery. Most of the chemotherapy records at RCCs/PMH were captured automatically at the point of prescription through the centers' electronic chemotherapy ordering systems and were, therefore, of high quality. Because a substantial proportion of chemotherapy (~50%) is delivered by medical oncologists who are not associated with RCCs/PMH, chemotherapy physician billing codes (as described earlier) were used to describe, in general terms, the use of ACT among all patients in Ontario. RCC/PMH centers are the only providers of RT in the province. Stage of disease at diagnosis is only captured routinely for patients seen at RCCs. The study was approved by the Research Ethics Board of Queen's University.

Definitions of Comorbidity, Management, and Outcomes

Comorbidity was classified using the Charlson Index modified for administrative data based on all noncancer diagnoses recorded on any hospital admission within 5 years before surgery.[12,13] Surgical resection was defined as pneumonectomy, lobectomy, or segmentectomy. Adjuvant therapy was defined as any chemotherapy or RT administered within 16 weeks after surgery.

As a surrogate for treatment-related toxicity, we used the Canadian Institute for Health Information database to identify all admissions to hospital (and their related ICD diagnoses) within 16 weeks of starting ACT. Admissions that were associated with ICD diagnoses of metastatic disease (i.e., metastases, pathologic fracture, and spinal cord compression) were excluded. ICD diagnostic codes for common chemotherapy-related toxicities were grouped into infectious, gastrointestinal, cardiac, fluid/electrolyte abnormalities, noninfectious respiratory, anemia, and venous thromboembolism categories. Deaths that were potentially related to ACT were defined as any death that occurred within 16 weeks of starting ACT that was not associated with any hospitalization ICD diagnostic code of metastatic disease as described earlier.

For each patient, an initial chemotherapy regimen was identified based on the first combination of drugs administered. Subsequent regimens within the 16-week time frame were classified as modified adjuvant regimens. Changes to drug dose were identified by change in dosage for any cytotoxic agent administered within 24 weeks of initiating ACT. Dose reductions were defined as a decrease in any one of the cytotoxic drugs administered, and omitted doses were identified by any treatment record with a dose of zero. Details related to carboplatin dosing were not included in this analysis as each treatment is dosed on individual creatinine clearance and therefore dose changes were less likely to reflect true dose modifications.

Statistical Analysis

Comparisons of proportions between study groups were made using the χ^2 test. Overall survival was determined from date of surgery using the Kaplan-Meier technique and comparisons between groups were made using the log-rank test. For comparative purposes, we reproduced survival

curves from the relevant meta-analyses[6,14] by measuring survival at regular intervals on the published plots. Factors associated with dose modification were evaluated were evaluated by logistic regression. Variables with $p < 0.1$ in univariate analysis were entered into the multivariate analysis. A stepwise selection technique was used with a significance level for entry and exit of $p = 0.1$. Predictors were considered statistically significant at $p < 0.05$. The Cox proportional hazards model was used to describe associations between patient-, disease-, and treatment-related factors and survival. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patterns of Care

As reported previously,[2] there was substantial uptake of ACT for NSCLC in Ontario from 2004 onward. Within the 2001–2006 study cohort ($n = 6304$), we identified 1224 patients (19%) who received ACT. ACT was primarily used in the postadoption cohort: 7% (192/2950) in 2001–2003 versus 31% (1032/3354) in 2004–2006 ($p < 0.0001$). During this study period, 4-year survival of all surgical cases (i.e., $n = 6304$) improved from 52.5% in 2001–2004 to 56.1% in 2004–2006 ($p = 0.001$). To describe use of ACT in the postadoption period, subsequent results pertain to cases diagnosed in 2004–2006 ($n = 3354$).

As shown in Figure 1, patients were identified as having ACT using two distinct chemotherapy data sources: OHIP physician billing records ($n = 1008$) and treatment records from RCCs/PMH ($n = 597$). Among the 597 cases identified as being treated with ACT at RCCs/PMH, we identified corresponding physician billing records for ACT in 573 (96%), suggesting that billing records for chemotherapy are very complete.

Characteristics related to the study population are described in Table 1. Among the 1032 patients who received ACT, 597 were treated at RCCs/PMH and 437 were treated outside a comprehensive cancer center. Compared with patients who did not receive ACT, those that received ACT were younger in age and had less comorbidity. The apparent difference in stage distribution observed between the two groups is likely confounded by the greater proportion of cases with ACT referred to a RCC. TNM stage is captured routinely only for cases seen at RCCs.

Delivery of ACT

Details regarding regimens used among cases diagnosed during the period 2004–2006 are shown in Table 2. Among the 597 cases with RCCs/PMH treatment records, a regimen name was identified in 98% (584/597). Almost all cases included cisplatin- or carboplatin-based regimens (478/584, 82%, and 99/584, 17%, respectively). Consistent with the relevant RCTs, the most common regimen was a vinroelbine/cisplatin doublet (412/584, 71%). In only a small proportion of cases (29/584, 6%) was the initial regimen changed. In many of these cases (10/29, 34%), the change in regimen reflected the substitution of carboplatin for cisplatin.

Among the 520 cases with drug dosages available for comparison, 56% of cases had at least one dose reduction or omission. Among patients treated with vinorelbine-cisplatin, 64% of cases had a dose reduction or omission. As shown in Table 3, the only variable independently associated with dose modifications was region of residence.

Outcomes

As previously reported,[2] the proportion of all cases admitted to hospital within 6 months of surgery did not change from 2001–2003 (36%) to 2004–2006 (37%), suggesting that there was no major increase in serious toxicity with the uptake of ACT. Among the 1032 cases that received ACT in 2004–2006, 16% (160/1032) were admitted to hospital with any diagnosis within 16 weeks of starting ACT; 12% (122/1032) of cases were admitted to hospital during the same time frame when hospitalizations associated with diagnostic codes for metastatic disease were excluded from the analysis. Among the latter cohort, the following diagnoses were commonly reported: infectious (65/122, 53%); gastro-

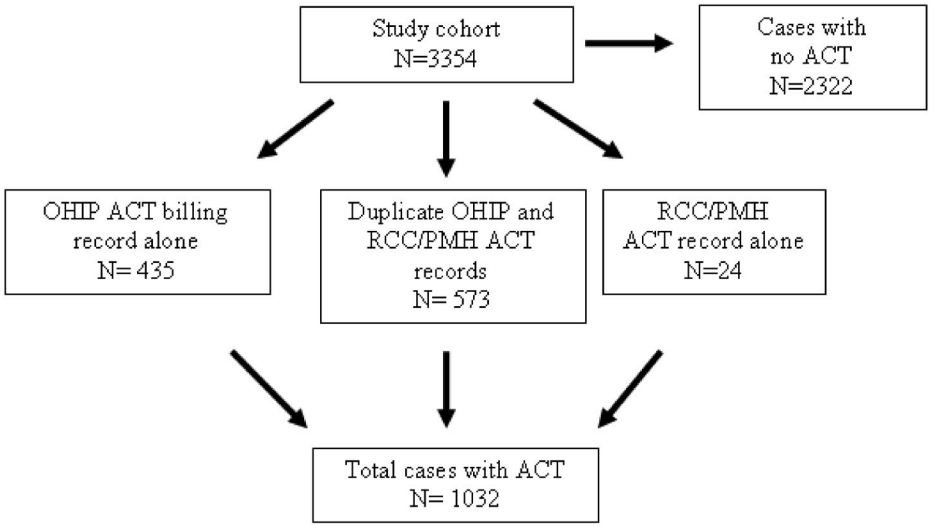


FIGURE 1. Identification of cases administered adjuvant chemotherapy (ACT) among all surgical cases of NSCLC diagnosed in Ontario 2004–2006 (n = 3354).-

TABLE 1. Characteristics of Patients Diagnosed with Non-small Cell Lung Cancer in Ontario 2004–2006 Who Underwent Surgical Resection (n = 3354)

	All Cases Who Underwent Surgery	
	ACT n = 1032 (31%)	No ACT n = 2322 (69%)
Characteristic	no. (%)[a]	
Patient-related		
Age, years		
20–49	100 (56)	80 (44)
50–59	293 (49)	308 (51)
60–69	398 (37)	680 (63)
70–79	229 (19)	996 (81)
80+	12 (4)	258 (96)
Sex		
Male	515 (30)	1203 (70)
Female	520 (32)	1119 (68)
SES, quintile[b]		
1	204 (29)	513 (72)
2	274 (35)	509 (65)
3	212 (30)	506 (71)
4	176 (30)	427 (71)
5	164 (31)	365 (69)
Charlson co-morbidity score		
0	821 (33)	1639 (67)
1–2	192 (25)	572 (75)
3+	19 (15)	111 (85)
Disease-related		
Histology		
Adenocarcinoma	558 (31)	1272 (70)
Squamous carcinoma	298 (29)	720 (71)
Large cell carcinoma	23 (32)	49 (68)
Mixed	37 (36)	65 (64)
Carcinoma NOS	116 (35)	216 (65)
Pathologic stage		
I	209 (36)	372 (64)
II	185 (66)	96 (34)
III	131 (61)	84 (39)
IV	48 (38)	80 (63)
Unknown	459 (21)	1690 (79)
Treatment-related		
Surgery		
Pneumonectomy	187 (47)	211 (53)
Lobectomy	600 (30)	1407 (70)
Segmentectomy	245 (26)	704 (74)
Median LOS following surgery	6 days	7 days
Referral to Regional Cancer Center	736 (40)	1084 (60)

[a]Percentages reflect proportion of cases in each category that had ACT. Percentages may not add to 100% due to rounding. Abbreviations: SES, socioeconomic status; NOS, not otherwise specified; LOS, length of stay

[b]SES quintile 1 represents patients from the poorest communities in Ontario.

intestinal (37/122, 30%); cardiac (33/122, 27%); fluid/electrolyte abnormalities (26/122, 21%); noninfectious respiratory (24/122, 20%); anemia (23/122, 19%); and venous thromboembolism (15/122, 12%).

TABLE 2. ACT Regimens Administered to 584 Cases Treated at RCCs/PMH from 2004 to 2006

	Frequency[a]
Use of cisplatin/carboplatin[b]	
Cisplatin-based	478 (82%)
Carboplatin-based	99 (17%)
No cisplatin or carboplatin	7 (1%)
Specific regimens[b]	
Vinorelbine/cisplatin	412 (71%)
Vinorelbine/carboplatin	27 (5%)
Carboplatin/paclitaxel	55 (9%)
Etoposide/cisplatin	45 (8%)
Other	45 (8%)
Regimen modification	
Change in drugs used	29 (6%)
Dose reduction[c]	144/520 (28%)
Omitted dose[c]	147/520 (28%)

[a] Denominator is 584 unless otherwise noted.

[b] Refers to regimen used in first cycle of ACT.

[c] Dose reduction and omitted doses were evaluated among the 520 cases for which drug dosage were identifiable from existing data sources.

Among the 1032 cases treated with ACT, there was a 3.1% (32/1032) death rate within 16 weeks of starting ACT; half of these (16/32) deceased cases had hospitalizations associated with ICD diagnostic codes for metastatic disease. This translates into a death rate that is potentially attributable to ACT of 1.6% (16/1032).

The survival curves shown in Figure 2 suggest that the outcome of those cases treated with adjuvant vinorelbine-cisplatin in the general population are very comparable with survival of patients from clinical trials as reported in two large meta-analyses.[6,14] The Cox analyses (Table 4) suggest that increased comorbidity, advanced stage of disease, and more extensive surgery are independently associated with worsened survival. Squamous cell histology was associated with improved survival. Dose modification was not found to be associated with inferior survival.

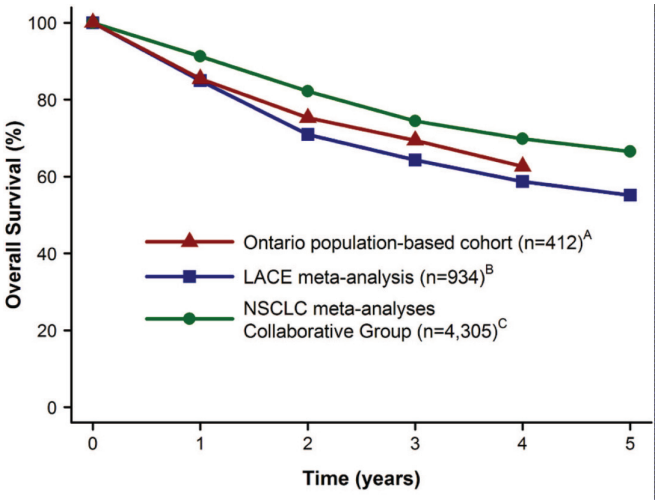
DISCUSSION

Clinical trials reported in 2004 led to substantial uptake of ACT in the Canadian province of Ontario. In this report, we describe details about what, how, and when ACT was administered in the "real world." From this large population-based study, several important findings have emerged. First, it is reassuring that the predominant regimen used in Ontario in the period 2004–2006 is vinorelbine-cisplatin for which the strongest clinical trial evidence exists. Second, compatible with the clinical trials, a substantial proportion of cases in the general population undergo dose and drug regimen modifications. Third, dose modification of ACT does not appear to be associated with inferior survival. Fourth, rates of hospitalization and death potentially attributable to ACT are consistent with those reported in RCTs. Finally, the survival of patients treated with ACT in the general population is comparable with survival of patients in clinical trials, lending further support to the effectiveness of therapy.

TABLE 3 Variables Associated with Dose Modification of Adjuvant Chemotherapy (ACT) for Non-Small Cell Lung Cancer Among 520 Cases with Bose Records Available Diagnosed in Ontario 2004–2006

Characteristic	Proportion Cases with Dose Modification	Univariate Analysis		Multivariate Analysis	
		OR (95%CI)	*P* Value	OR (95%CI)	*P* Value
Patient-related					
Sex					
Male (n = 270)	56%	Ref		—	—
Female (n = 250)	56%	0.97 (0.69–1.38)	0.873	—	—
Age, years					
20–49 (n = 53)	55%	Ref		—	—
50–59 (n = 144)	56%	1.03 (0.55–1.95)	0.916	—	—
60–69 (n = 209)	57%	1.12 (0.61–2.05)	0.723	—	—
70+ (n = 114)	54%	0.99 (0.51–1.90)	0.968	—	—
Socioeconomic status, quintile					
1 (n = 121)	55%	Ref		—	—
2 (n = 144)	53%	0.93 (0.57–1.51)	0.774	—	—
3 (n = 97)	61%	1.29 (0.75–2.23)	0.352	—	—
4 (n = 83)	57%	1.09 (0.62–1.91)	0.769	—	—
5 (n = 75)	57%	1.12 (0.63–2.00)	0.703	—	—
Charlson co-morbidity score					
0 (n = 414)	54%	Ref		—	—
1–2 (n = 96)	64%	1.48 (0.94–2.34)	0.094	—	—
3+ (n = 10)	60%	1.27 (0.35–4.58)	0.712	—	—
Disease-related					
Histology					
Adenocarcinoma (n = 268)	53%	Ref		—	—
Squamous carcinoma (n = 164)	61%	1.39 (0.93–2.06)	0.105	—	—
Large cell carcinoma (n = 13)	69%	2.00 (0.60–6.64)	0.260	—	—
Mixed (n = 12)	67%	1.78 (0.52–6.04)	0.358	—	—
Carcinoma NOS (n = 63)	51%	0.92 (0.53–1.59)	0.754	—	—
Pathologic stage					
I (n = 162)	61%	Ref		—	—
II (n = 149)	51%	0.66 (0.42–1.04)	0.073	—	—
III (n = 98)	58%	0.89 (0.53–1.47)	0.638	—	—
IV (n = 26)	50%	0.64 (0.28–1.46)	0.287	—	—
Unknown (n = 85)	54%	0.75 (0.44–1.28)	0.290	—	—
Treatment-related					
Surgery					
Lobectomy (n = 336)	55%	Ref		—	—
Pneumonectomy (n = 91)	63%	1.40 (0.87–2.26)	0.164	—	—
Segmentectomy (n = 93)	55%	1.02 (0.64–1.61)	0.949	—	—
Length of hospital stay					
<Median (n = 283)	57%	1.12 (0.79–1.59)	0.520	—	—
>Median (n = 237)	54%	Ref		—	—
Geographic region of Ontario					
A (n = 64)	44%	Ref		Ref	
B (n = 87)	58%	1.74 (0.91–3.33)	0.097	1.74 (0.91–3.33)	0.096
C (n = 98)	47%	1.14 (0.60–2.14)	0.691	1.14 (0.60–2.14)	0.691
D (n = 70)	73%	3.45 (1.68–7.11)	<0.001	3.45 (1.68–7.11)	<0.001
E (n = 29)	66%	0.63 (0.38–1.03)	0.055	0.63 (0.38–1.03)	0.055
F (n = 31)	39%	0.81 (0.34–1.95)	0.641	0.81 (0.34–1.95)	0.641
G (n = 35)	54%	1.53 (0.67–3.50)	0.317	1.53 (0.67–3.50)	0.317
H (n = 106)	62%	2.12 (1.13–3.99)	0.020	2.12 (1.13–3.99)	0.020

Note: Percentages may not add to 100% due to rounding.
Abbreviations: RR, relative risk; Ref, reference group; SES, socioeconomic status; NOS, not otherwise specified.



A: Ontario cohort: Booth et al 2011
B: LACE meta-analysis: Douillard et al J Thorac Onc 2010
C : NSCLC meta-analyses Collaborative Group; Arriagada et al Lancet 2010.

FIGURE 2. Reported survival of NSCLC cases treated with vinorelbine-cisplatin adjuvant chemotherapy.

Contemporary RCTs which established the role of ACT for NSCLC include IALT, NCIC CTG JBR.10, the ANITA trial, and Cancer and Leukemia Group B (CALGB) 9633.[1] Adjuvant vinorelbine-cisplatin led to improved outcomes in both JBR.10 and the ANITA trial, with absolute improvements in survival of 15% and 9% at 5 years, respectively.[3,4] Both trials used a 28-day regimen in which patients where given 25 to 30 mg/m^2 of vinorelbine weekly and 100 mg/m^2 of cisplatin per cycle. In JBR.10, cisplatin was given in two divided doses on days 1 and 8. These regimens were associated with substantial hematologic toxicity with most of patients experiencing dose reductions and/or omissions. Only 50% (108/215) of patients in JBR.10 completed four cycles of therapy, and 77% had at least one dose reduction or omission.[3,7] It is important to note that the impressive survival benefit in both JBR.10 and ANITA was seen despite the relatively high rates of hematologic toxicity and low-dose delivery.

Data from this study suggest that dose modification is also common among patients in the general population. The rate of dose reductions and omissions in the general population is comparable to figures reported in JBR.10. However, limitations of existing treatment records in our population-based study may lead to an underestimation of dose omissions. In any case, we have observed comparable outcomes in the general population despite frequent dose reductions and omissions.

CALGB 9633 evaluated paclitaxel and carboplatin in patients with stage IB disease. Although initial results presented in 2004[15] showed a 12% absolute improvement in survival at 4 years, when mature data were presented in 2006 the difference was no longer statistically significant.[16,17] We did observe that a substantial number of patients were treated with carboplatin-paclitaxel during the study period when existing evidence supported use of this regimen. Ongoing research will explore whether use of adjuvant carboplatin-paclitaxel declined after updated results of CALGB 9633 were presented in 2006. Our data also suggest that carboplatin is used in the general population as a substitute for cisplatin (25 patients received vinorelbine-carboplatin). It is likely that this reflects treatment of patients with renal insufficiency, hearing deficits, or neuropathy who would not be eligible for cisplatin. These patients routinely are excluded from clinical trials yet represent a sizable proportion of patients in the general population. Further work is needed to identify whether these patients benefit from ACT and what regimens should be used.

As reported previously,[2] the proportion of NSCLC surgical cases admitted to hospital did not increase from 2001–2003 to 2004–2006, coincident with the adoption of ACT suggesting no major increase in patient toxicity. Among the 1032 cases treated with ACT in 2004–2006, we observed rates of hospitalization (12%) and death (1.6%) that are very comparable to those reported in the ACT arm of JBR.10 (19% hospitalization; 0.9% death rate) and ANITA (hospitalization not reported; 2% death rate).[3,4]

Translation of knowledge from RCTs into societal benefit relies on the novel therapy being adopted by practitioners and whether the results of the clinical trial are generalizable to the overall population. Because patients, physicians, and concurrent care in the general population may be very different from the controlled context of a clinical trial, it is essential that we not assume that the benefits demonstrated in phase 3 studies will be fully realized at the population level. It is therefore reassuring that the survival of patients treated in the general population is very comparable to survival observed in the relevant clinical trials. Although RCTs have clearly established efficacy for ACT in NSCLC, this population-based study lends support to the effectiveness of ACT in the "real world."

Although this study is the largest and first comprehensive report to provide detailed-treatment information for patients administered ACT in the general population, several methodologic limitations merit comment. Although the data sources used in this study describe general aspects of disease, treatment, and outcome for all patients in Ontario, detailed information related to chemotherapy administration, treatment toxicity, performance status, and stage of disease is not available for all patients. This limits our ability to evaluate the appropriateness of case selection for ACT and also makes it difficult to determine with certainty the relationship between time from surgery to initiation of ACT and outcome. Incomplete records regarding dosing of ACT have limited our ability to provide detailed information on dose intensity and its impact on outcome. Furthermore, treatment details related to drug regimen and dose are only available for those patients treated at a RCC and therefore may not represent practice at hospitals not affiliated with a cancer center. Finally, we have used rates of hospitalization as a surrogate for the most serious toxicity related to ACT. Trends in rates of hospitalization may be confounded by changes of practice regarding in-patient care and greater use of community resources.

TABLE 4 Variables Associated with Survival Among 1032 Patients with Non-Small Cell Lung Cancer Treated with Adjuvant Chemotherapy in Ontario 2004–2006

		Univariate Analysis		Multivariate Analysis	
Characteristic	**OS at 4 Years**	**HR (95%CI)**	*P* Value	**HR (95%CI)**	*P* Value
Patient-related					
Sex					
Male (n = 515)	55%	Ref		Ref	
Female (n = 517)	60%	0.78 (0.63–0.95)	0.015	0.82 (0.66–1.02)	0.070
Age, years					
20–49 (n = 100)	60%	Ref		Ref	
50–59 (n = 293)	62%	0.82 (0.56–1.20)	0.316	0.86 (0.59–1.26)	0.433
60–69 (n = 398)	57%	0.95 (0.66–1.36)	0.758	0.92 (0.63–1.33)	0.651
70+ (n = 241)	52%	1.16 (0.80–1.69)	0.442	1.17 (0.79–1.73)	0.427
Socioeconomic status, quintile					
1 (n = 204)	58%	Ref		Ref	
2 (n = 274)	57%	1.02 (0.76–1.37)	0.895	1.02 (0.75–1.37)	0.924
3 (n = 212)	53%	1.04 (0.76–1.41)	0.828	1.05 (0.77–1.44)	0.747
4 (n = 176)	58%	0.93 (0.67–1.30)	0.680	0.90 (0.64–1.26)	0.536
5 (n = 164)	64%	0.88 (0.62–1.25)	0.474	0.80 (0.56–1.14)	0.221
Charlson co-morbidity score					
0 (n = 821)	58%	Ref		Ref	
1–2 (n = 192)	55%	1.18 (0.92–1.52)	0.205	1.18 (0.91–1.53)	0.214
3+ (n = 19)	42%	2.00 (1.09–3.64)	0.025	2.10 (1.14–3.88)	0.018
Disease-related					
Histology					
Adenocarcinoma (n = 558)	56%	Ref		Ref	
Squamous carcinoma (n = 298)	63%	0.93 (0.73–1.18)	0.528	0.74 (0.57–0.95)	0.021
Large cell carcinoma (n = 23)	46%	1.20 (0.64–2.27)	0.567	1.24 (0.65–2.36)	0.509
Mixed (n = 37)	54%	1.16 (0.68–2.00)	0.588	1.00 (0.58–1.73)	0.997
Carcinoma NOS (n = 116)	55%	1.37 (1.00–1.86)	0.049	1.12 (0.81–1.54)	0.490
Pathologic stage					
I (n = 209)	75%	Ref		Ref	
II (n = 185)	48%	2.29 (1.59–3.29)	<0.001	2.17 (1.50–3.14)	<0.001
III (n = 131)	46%	2.67 (1.82–3.91)	<0.001	2.33 (1.58–3.44)	<0.001
IV (n = 48)	31%	5.52 (3.50–8.72)	<0.001	4.89 (3.04–7.88)	<0.001
Unknown (n = 459)	59%	1.73 (1.24–2.40)	0.001	1.48 (1.02–2.14)	0.038
Treatment-related					
Surgery					
Lobectomy (n = 600)	60%	Ref		Ref	
Pneumonectomy (n = 187)	50%	1.62 (1.26–2.1)	<0.001	1.52 (1.17–1.99)	0.002
Segmentectomy (n = 245)	57%	1.1 (0.85–1.40)	0.518	0.96 (0.74–1.24)	0.762
ACT dose modification					
No dose modification (n = 229)	62%	Ref		Ref	
Dose modification (n = 291)	57%	1.06 (0.79–1.42)	0.719	1.07 (0.80–1.44)	0.651
Unknown (n = 512)	56%	1.09 (0.83–1.41)	0.566	1.21 (0.88–1.66)	0.242

Abbreviations: OS, overall survival; HR, hazard ratio; Ref, reference group; SES, socioeconomic status; NOS, not otherwise specified; ACT, adjuvant chemotherapy.

In addition to its very large sample size and resulting statistical power, a major strength of the current study is the fact that by virtue of the OCR, our study population includes all cases of NSCLC within Ontario and is therefore unselected. By including the entire population of interest, it is possible to minimize the referral and selection biases that plague traditional institution-based observational studies.[18] In fact, we describe use of ACT among 1032 patients in Ontario and have detailed records for the 584 cases treated at comprehensive cancer centers. This represents a large sample of patients when one considers that 242 and 407 patients were randomized to receive ACT in the JBR.10 and ANITA trials, respectively.

In summary, the outcomes associated with ACT for NSCLC in the general population are comparable to those reported in clinical trials. It is reassuring that the rates of hospitalization and on-treatment mortality in the general population are not substantially different from those reported

in RCTs. Furthermore, although dose modifications of ACT are common, they do not seem to be associated with inferior outcome. Further research is needed to identify appropriateness of ACT utilization in the general population.

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